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Message from the Scientific Director

As I write this, at the end of April, the world is once again facing the possibility of an influenza pandemic – an eventuality we were certainly not expecting when we scheduled this newsletter several months ago. But H1N1 influenza continues to spread and the World Health Organization has raised its pandemic alert level to Phase 5, marking human-to-human transmission in the community.

Fortunately, Canada is prepared to meet the challenges if this outbreak does, indeed, transform into a pandemic. This is in no small part due to the foresight of the Government of Canada in allocating $21.5 million over 5 years for pandemic research. In response, the Institute of Infection and Immunity launched the Pandemic Preparedness Strategic Research Initiative (PPSRI) in 2006, at a time when an avian flu pandemic was thought to be imminent. Thanks to the contributions of our partners, we have since been able to devote over $40 million to pre-pandemic and outbreak-focused projects.

Today, under the umbrella of the PPSRI, Canada's research community is ready to act. Guy Boivin from Laval University has been identified to bring together a national network for characterization of influenza virus evolution and antiviral susceptibility, while Babak Pourbohloul of the University of British Columbia is the Pandemic Outbreak Team Leader in Mathematical Modeling. CIHR and the Public Health Agency of Canada (PHAC) have expedited the funding process to ensure these initiatives are able to meet the challenge of establishing the research programs rapidly.

CIHR-III has also taken steps as part of the PPSRI Outbreak Strategy: We have requested updates on funded projects, outbreak research plans and any results that can be communicated to those on the front lines. We are organizing teleconferences on priority areas to facilitate research collaboration, coordination and sharing of specimens and reagents. Following peer review, funding for the Influenza Research Network has been recently approved. And our PPSRI Task Group is meeting weekly to review research strategies and respond to evolving issues. As for SARS, the Institute is again mobilizing the Canadian research response to an emerging infectious disease.

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We have learned from our experience with the SARS outbreak in 2003 the importance of a rapid research response to help battle outbreaks and keep them from spreading. On an ongoing basis, we are supporting important research to better protect Canadians and people around the world from a pandemic. The innovative projects profiled in this issue of Microcosm-III illustrate the complexity of planning for a pandemic, the important role of research in every aspect of a pandemic response and the multidisciplinary approach that is necessary to ensure we are prepared.

A strategic and timely investment has indeed built the critical mass of researchers who are ready and willing to address the pandemic challenge. As the influenza outbreak progresses, it is heartening to see the research community working together to respond quickly and effectively.

Bhagirath Singh, PhD
Scientific Director
CIHR Institute of Infection and Immunity

III Reports

Models to Investigate the Link Between the Mucosal Immune Response in the Lung and Respiratory Tract and Disease Outcomes

Humans are in constant contact with millions of microbes, including both infectious and non-infectious pathogens. The initial site of exposure, and our first line of defence, is often the mucosal immune system in the lung – a particularly important and understudied site of pathogen/host interaction. In an attempt to better understand this system, the CIHR Institute of Infection and Immunity (CIHR-III), in partnership with the CIHR Institute of Circulatory and Respiratory Health, AllerGen and the Canadian Cystic Fibrosis Foundation (CCFF), launched a Request for Applications (RFA) entitled "Models to Investigate the Link Between the Mucosal Immune Response in the Lung and Respiratory Tract and Disease Outcomes." A report is now available on the institute website (www.cihr-irsc.gc.ca/e/39285.html) that describes some of the outcomes and research discoveries that correspond to the original five objectives of the initiative.

Funding Opportunities

The CIHR Institute of Infection and Immunity is dedicated to supporting research and building research capacity in the areas of infection and immunity. For more information about the full list of current funding opportunities offered by III, visit the III home page (www.cihr.gc.ca/iii.html) and click on the "III Funding Opportunities" link on the top right menu. Most opportunities are released in June and December of each year.

New opportunity, off-cycle launch:

- Emerging Team Grant: HIV/AIDS Vaccine Discovery and Social Research

Funding Decisions

The following funding decisions have been announced over the previous months. Consult the CIHR website for full details (http://www.cihr-irsc.gc.ca/e/38649.html).

May 2009

- Other: Influenza Research Network

April 2009

- Meetings, Planning and Dissemination Grant: Infection and Immunity
- Training Grant: 2007-2008 (Strategic Training Initiative in Health Research)

March 2009

- Catalyst Grant: HIV/AIDS (Community-Based Research) (2008-2009)
- Catalyst Grant: Human Microbiome
- Catalyst Grant: Safe Food and Water in Northern Communities
- Catalyst Grant: Systems Biology Approaches to Immunotherapy
- Doctoral Research Award: HIV/AIDS (Community-Based Research) (2008-2009)
- Master's Award: HIV/AIDS (Community-Based Research) (2008-2009)
- Operating Grant: HIV/AIDS (Community-Based Research) (2008-2009)
- Other: Capacity Building Workshop in HIV/AIDS (Community-Based Research) (2008-2009)
- Other: Research Facilitators in HIV/AIDS (Community-Based Research) (2008-2009)

February 2009

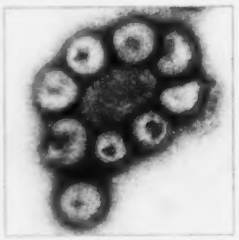
- Catalyst Grant: HIV/AIDS Vaccine Discovery Research
- Catalyst Grant: Pandemic Preparedness

January 2009

- Catalyst Grant: Pandemic Outbreak Team Leader
- Operating Grant: Fall 2008 Priority Announcement – CIHR Institute of Infection and Immunity (Bridge Funding)
- Operating Grant: Fall 2008 Priority Announcement – Hepatitis C (Bridge Funding)
- Operating Grant: Fall 2008 Priority Announcement – HIV/AIDS (Bridge Funding)
- Operating Grant: Fall 2008 Priority Announcement – HIV/AIDS

CIHR-III congratulates Dr. Gregor Reid of the University of Western Ontario and Dr. Sylvain Moineau of Laval University, who are collaborators on projects recently funded through the International Science and Technology Center (ISTC) in Moscow, Russia. Their research focuses on probiotics and bacteriophage respectively, and the current collaborations are a result of a joint initiative of CIHR-III and Department of Foreign Affairs and International Trade Canada (DFAIT) in 2006 to expand research collaborations between Canada and Russia.

Pandemic Preparedness



H1N1 Influenza*

In 2006, the CIHR Institute of Infection and Immunity was charged with developing and supporting pandemic influenza preparedness research programs, as part of the government of Canada's Avian Influenza and Pandemic Influenza Preparedness Strategy. The Pandemic Preparedness Strategic Research Initiative (PPSRI) was the result, a five-year program to support research intended to improve Canada's ability to prevent and/or respond to an influenza pandemic. Strategic priorities for the Initiative were:

- Capacity building;
- Vaccines and immunization programs: optimal use and efficiency of existing vaccines and development of new pandemic vaccines;
- The virus: biology of the influenza virus and rapid diagnostics;
- Prevention and treatment: modes of transmission, use of antivirals and alternate strategies for prevention; and
- Ethics, legal and social research: risk communication, prioritization and the regulatory approval process.

These priorities were translated into a series of funding opportunities, beginning in fall 2006, that included operating grants, catalyst grant, team funding, knowledge synthesis grants and grants associated with other CIHR-wide programs, such as the Partnerships for Health System Improvement program and the China-Canada Joint Health Research Initiative.

PPRSI by the numbers
Number of identified research priorities: 5
Number of partners with formal partnership agreements: 4
Amount contributed by partners: $16 million
Number of funding opportunities launched: 30
Number of applications received: 149
Number of funded applications: 71

Partners have played a key role in the PPRSI. They have been involved in setting priorities for the Initiative, assessing relevance of proposals and participating in peer review. Their involvement enabled coordination and integration of research across Canada. In addition, partners' contributions have added $18.5 million to the original $21.5 million allocated to the initiative. Partners include the Public Health Agency of Canada, the Canadian Food Inspection Agency, the Rx&D Health Research Foundation and the International Development Research Centre, as well as several CIHR Institutes.

A mid-term evaluation of the PPRSI found that the creation of the PPRSI contributed to significantly more funding allocated to pandemic-related research. It also found that:

* *Image of a number of H1N1 Influenza Virus particles © Dr. F. A. Murphy, Centers for Disease Control and Prevention, 1600 Clifton Rd, Atlanta, GA 30333, U.S.A.*

- THE PPSRI IS CURRENTLY ENGAGING AN ESTIMATED 150 AND 200 TRAINEES IN PANDEMIC PREPAREDNESS RESEARCH, CONTRIBUTING TO GREATER RESEARCH CAPACITY IN THIS AREA;
- PPRSI HELPED TO ENHANCE COLLABORATION BY PROVIDING RESEARCHERS WITH NETWORKING OPPORTUNITIES AND BUILDING TIES BETWEEN GOVERNMENTS AND UNIVERSITIES AND BETWEEN ANIMAL AND HUMAN RESEARCHERS; AND
- PPSRI'S PROGRAM DESIGN CREATED A PLATFORM FOR A NATIONAL PANDEMIC PREPAREDNESS RESEARCH AGENDA THAT IS MUCH MORE COORDINATED THAN IT WOULD HAVE BEEN IN THE ABSENCE OF THE PPRSI.

The evaluation's overall conclusion is that the PPSRI's design, delivery and initial outputs are ensuring that its goals of improving Canada's pandemic preparedness and increasing research capacity in the area can be met. It found that PPRSI has been especially successful in developing solid and productive partnerships, developing consensus on research priorities and implementing tools to address these priorities, providing a solid foundation for future success.

PPSRI Researchers: Profiles in Preparedness

André Dascal, Georges Dionne, Louise Rousseau, Nicolas Béland

Ability and willingness of health-care workers to report for work in an influenza pandemic

Robert Maunder

Education and support to increase the resilience of healthcare workers facing pandemic influenza: What is the minimum effective dose?

What if you threw a pandemic – and no one came?

Dr. André Dascal

That's Dr. André Dascal's concern. He believes that, due to a combination of inability and unwillingness, a proportion of health-care workers — including physicians, nurses, allied health professionals and support staff — just may not show up on the job in the case of a pandemic. And that could seriously harm our ability to provide the needed care to people stricken with influenza during a pandemic, whether in institutions or in the community.

For Dr. Dascal, of the Sir Mortimer B. Davis Jewish General Hospital in Montreal, in addition to being unable to report for work because of issues such as unavailable child care, transportation, etc., risk perception plays an important role. He, along

with his co-investigators, has conducted quantitative and qualitative surveys of health-care workers to find out more about their perceptions of, and responses to, risk, in addition to other barriers to reporting to work in a pandemic.

"Evaluating risk-taking is a very difficult area to assess," says Dr. Dascal. "But that's what makes this study different."

Dr. Dascal hopes that the results of the surveys will assist in better understanding those who will, or will not, continue to show up at work during a pandemic. The team is now analyzing the results of those surveys and, once they have their conclusions, they will focus on sharing their results with health care administrators.

"We'll start with the professional bodies that helped us with the surveys," he says. "They will have a huge role to play."

Other targets for sharing results will include Montreal public health officials as well as officials with the Quebec Ministry of Health and Social Services.

Armed with his results, Dr. Dascal hopes to take his research a step further by developing interventions that could help overcome the unwillingness of some health-care workers to work during a pandemic. And, when he reaches the point of designing interventions, he could speak with Bob Maunder.

Dr. Maunder is a psychiatrist and researcher at Toronto's Mount Sinai Hospital. His research normally focuses on inflammatory bowel disease but, in the wake of the SARS outbreak of 2003, he took a slight detour, working with his colleague, Dr. Bill Lancee to look at the persistence of stress among health-care workers long after the outbreak was over.

Dr. Robert Maunder

"The stress of an infectious disease outbreak is different from other natural disasters," he says. "People are isolated, because of stigma and the precautions taken to minimize the spread of the disease."

Drs. Maunder and Lancee looked at the sources of stress – for instance, those who felt they were well-trained and well-supported during the outbreak were doing much better a year or two later than their colleagues – as well as its impacts, such as people drinking or smoking more or experiencing more interpersonal stress. And this gave them important clues about where to focus efforts to reduce loss of health-care workers to stress during a pandemic. The problem is, the best methods for alleviating stress and providing support, such as coaching and workshops, are very resource intensive. So Drs. Maunder and Lancee set out to design an intervention that could provide the support health-care workers need on a large scale.

The intervention they developed is a com-

puterized training course that comes in modules. Some are standard teaching modules. Others, however, present videos of scenarios and ask participants to reflect on their responses to those scenarios.

"The cool part is we used actors to simulate scenarios we would expect to be stressful for health-care workers," says Dr. Maunder. "Then we pose questions about the worker's response to the scenario and, depending on the response, they are led to a different set of reflections appropriate to their response."

Drs. Maunder and Lancee are also trying to find out how much of this sort of training is enough, by producing short, medium and long versions of the tool. They are finding that the long is too long, the short a bit too short, but that the medium could be just right. And they are comparing the effectiveness of his intervention to traditional coaching and workshops. If it proves to be effective, they will make the technology available to others and encourage them to develop their own scenarios appropriate to their settings.

As Dr. Dascal notes, the SARS outbreak lasted some four months. A pandemic could last much longer, making it even more essential that health-care workers are supported so that they can continue to provide care to affected Canadians.

Janet E. McElhaney

The roadmap to improved correlates of protection against influenza

Dr. Janet E. McElhaney

Influenza is one of the six leading causes of catastrophic disability among older adults, often leading to the loss of independence. Yet existing influenza vaccines don't result in the same level of immunity among this vulnerable population as they do among healthy young adults.

Part of the problem is that, until now, there has been no way to effectively assess just how much immunity a vaccine produces among older adults. But Dr. Janet McElhaney of the Vancouver Coastal Health Research Institute has developed a way to do so that could lead to improved protection for vulnerable populations against influenza.

Existing vaccines are assessed based on the level of antibodies they produce, which works well for young, healthy adults. But this assessment doesn't provide the same information about immunity in older adults. Dr. McElhaney has developed and tested an assay that measures

immunity using other markers, including granzyme B and the IFN gamma/IL-10 ratio, both of which are related to T-cell activity. She has validated the ability of the assay to effectively act as a surrogate for assessing immunity. Now she is working with partners in Europe, the United States and Canada on a larger project to find other correlates that could be effective markers of immunity.

Her research could help protect older adults from the catastrophic effects of influenza. It could also lead to better ways to ensure vaccines protect their intended targets sooner in the vaccine development process.

Currently, vaccines are tested in animal models, before moving on to testing in healthy young adult humans. The testing isn't extended to other, more vulnerable, groups until much later in the testing process.

"We're way down the pipeline in vaccine development before we can get an idea of whether they'll work in older adults," she says. "This is a huge financial risk – you can be in phase III clinical trials before you realize that what you're testing is no better than what we have right now."

The assay Dr. McElhaney has developed means that vaccines can be tested for their effectiveness in older adults – and potentially in other vulnerable populations, such as small children – long before clinical testing in humans. And that means that the people who are affected most seriously by influenza, whether avian or otherwise, will be better protected in the case of a pandemic.

David Buckeridge

Assessing the population effect of a new vaccination policy: An international comparison

It's a risky undertaking, David Buckeridge says. But if it's successful, it will open up new avenues for pandemic influenza research.

The project, which he is undertaking with Harvard University colleague Dr. John Brownstein, is looking at what happens when immunization policy for influenza expands from just infants 6-23 months to include all children under five. That's what happened in the United States, while the immunization recommendation in Canada remained focused on infants. The result was a perfect natural experiment, a laboratory to find out whether the divergence in policy results in different outcomes.

The problem is that individual-level data on vaccination are not readily available in Canada. It would be easier to do this kind of survey with individual-level data. But it would also be a lot more costly to gather those data. So Drs. Buckeridge and Brownstein are trying to demonstrate the extent to which the more-readily available population-level health-care services data can be used to learn about the epidemiology of influenza. For instance, in a previous study, Dr. Buckeridge compared hospital admissions data with outpatient billing data in Quebec and stratified it by age group. He found that in 2001-2002, health-care services use by children under age 13 began earlier than in other years. That year, an influenza strain reappeared that hadn't been seen in Quebec for 13 years, meaning that those under 13 had no natural immunity to it. Now, Drs. Buckeridge and Brownstein are comparing Canadian and American data to see if they can draw any conclusions about the merits of immunizing children aged 2-5 years of age.

"We knew that relying on health services data for this study was high-risk from the start," says Dr. Buckeridge, a researcher from McGill University. "The best we can do without individual-level vaccination data is to obtain rough estimates. But we should be able to learn enough to make a compelling case for further studies using higher-quality data."

The immunization policy difference is more than a simple change – it involves a different way of thinking about immunization. In Canada, says Dr. Buckeridge, the thinking is still about risk groups – targeting those at greater risk of bad outcomes following infection. In the United States, they are also focusing on groups like older children, not because they are at greater risk of bad outcomes, but because of their potential for spreading infection.

"That's a big shift in thinking," Dr. Buckeridge points out. "It's one thing to say you need immunization because you're at risk personally. It's another to say that you need immunization because you're a risk to others. It's a real ethical dilemma and that's the debate we're trying to inform with this study."

Dr. Buckeridge likens the situation to Ontario's decision to require health-care workers to be immunized against influenza. But, he adds, the evidence there of the risk that they pose to others is very strong. The evidence is weaker for the risk posed by older children. His work could help provide stronger evidence of the risks and benefits of the American vs. the Canadian approach.

Meetings and Events

The following meetings may be of interest to the III community:

- Canadian Society of Microbiologists (CSM) Annual Conference, June 15-18, 2009, Concordia University, Montreal, QC, Canada (http://csm2009.concordia.ca/)
- Association of Medical Microbiology and Infectious Disease (AMMI) 2009 Annual Conference, June 18-21, 2009, Sheraton Centre Toronto, Toronto, ON, Canada (http://www.ammi.ca/annual_conference/index.php)
- Canadian Pandemic Preparedness Meeting: From Discovery to Frontlines, Fall 2009, Toronto (For more information, contact Michelle Hume)
- Canadian Society for Immunology (CSI) Spring 2010 Meeting, April 23-26, 2010, Sheraton on the Falls, Niagara Falls, ON, Canada (http://www.csi-sci.ca/scientificmeeting/meetingwelcome10.aspx)

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